High-dose, pulsatile erlotinib after progression on standard dose erlotinib in EGFR-mutated NSCLC patients

Published: 06-09-2012
Last updated: 15-05-2024

see whether this treatment schedule is effective in EGFR-mutated NSCLC patients who have developed progression after treatment with EGFR-TKI monotherapy in standard dose before

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON36916

Source
ToetsingOnline

Brief title
Pulsatile erlotinib

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: erlotinib, high-dose, NSCLC, progression

Outcome measures

Primary outcome

To assess the disease control rate (DCR) at 8 weeks according to the response

evaluation criteria in solid tumors (RECIST v1.1)

Secondary outcome

- To assess progression-free survival (PFS)

- To assess toxicity of high-dose erlotinib according to CTC AE 4.0.

Study description

Background summary

Standard dose and schedule for erlotinib is 150 mg daily. However, different dosing schedules have been evaluated, in which pulsatile doses up to 2000 mg have been evaluated tolerable and with acceptable toxicity profile. This weekly, high-dosing schedule has been described in several case reports as therapeutic option for patients with leptomeningeal metastases. One group retrospectively analysed a series of 9 patients.

Toxicity of high-dose, pulsatile erlotinib
Known side effects of erlotinib in the standard, daily 150 mg dosing schedule comprise rash, diarrhoea, fatigue, nausea and/or emesis, stomatitis, weight loss, dehydration, pneumonitis and elevated liver values. Side effects of the higher-dose, weekly schedule are similar to the daily, standard dosing schedule. One study evaluated erlotinib in doses of 1200 mg, 1600 mg and 2000 mg. The dosing schedule of 1600 mg showed three grade 2 toxicities; one patient with grade 2 diarrhoea, one patient with grade 2 fatigue and one patient with grade 2 nausea and/or emesis. Nine patients reported grade 1 toxicities, of which most reported rash and diarrhoea.

Rationale
Since there are no other therapeutic options for patients with leptomeningeal metastases from EGFR-mutated NSCLC and toxicity of the high-dose pulsatile dosing schedule seems acceptable, we have treated several patients from our

department with this schedule. One patient treated with this schedule caught our special attention. It was a female patient of 51 years old with EGFR-mutated NSCLC who had been treated with EGFR-TKI*s since 2007, including erlotinib in combination with sorafenib, single agent erlotinib and afatinib in combination with cetuximab. After progression on the latter regimen she was treated with 2 cycles of cisplatin and pemetrexed. A CT-scan showed disease stabilisation of the intrathoracic disease but she developed leptomeningeal metasases. It was decided to treat her with erlotinib 1500 mg once weekly and maintain cytotoxic chemotherapy. Surprisingly after 3 weekly doses of the high dose erlotinib regimen there was significant decrease of the intrathoracic disease. Also, her neurological symptoms improved dramatically.
Although the molecular background of the tumor of this patient is unknown, approximately 50% of patients with an activating EGFR mutation harbour secondary mutations in particular the T790M mutation. The net result of this mutation is an increase in affinity of the EGF receptor for ATP thereby restoring signal transduction through this pathway. Since erlotinib is a competitive inhibitor of EGF signalling, in theory higher dose of the drug might restore sensitivity for the drug in this (common) situation.
We would like to evaluate prospectively whether this high-dose, weekly schedule of erlotinib shows activity in EGFR-mutated NSCLC patients that have developed systemic progression of disease. Since toxicity of this higher dose of erlotinib has been reported to be acceptable, we think that it is justified to evaluate this relatively simple dosing schedule in this group of patients.

Study objective

see whether this treatment schedule is effective in EGFR-mutated NSCLC patients who have developed progression after treatment with EGFR-TKI monotherapy in standard dose before

Study design

Single-arm, open-label phase II study

Intervention

erlotinib 1500 mg once every week

Study burden and risks

Risks include side-effects of the treatment schedule.

Contacts

Public
Vrije Universiteit Medisch Centrum

Boelelaan 1117
Amsterdam 1007MB
NL
Scientific
Vrije Universiteit Medisch Centrum

Boelelaan 1117
Amsterdam 1007MB
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Histologically confirmed stage IV non-squamous NSCLC patients.
* Patients with an activating EGFR mutation who progressed on erlotinib or gefitinib monotherapy in daily dose of 150 mg or 250 mg respectively. (Patients with unknown mutation status that have exhibited a response to these agents or stable disease for at least 6 months while on treatment with gefitinib or erlotinib are also eligible).
* Tumor biopsy available for EGFR mutation analysis at progression
* At least one measurable disease site, according to RECIST 1.1 criteria.
* WHO performance status 0-2.
* Willing and able to comply with the study prescriptions
* 18 years or older.
* Not pregnant or breast feeding and willing to take adequate contraceptive measures during the study.

* Ability to give and having given written informed consent before patient registration.

Exclusion criteria

Uncontrolled infectious disease.
Other active malignancy.
Major surgery (excluding diagnostic procedures like e.g. mediastinoscopy or VATS biopsy) in the previous 4 weeks.
Treatment with investigational drugs.
Known prior hypersensitivity to erlotinib.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-10-2012
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tarceva
Generic name:	erlotinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	06-09-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-09-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 20474
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2012-002951-40-NL
CCMO	NL41220.029.12
OMON	NL-OMON20474